AMENDMENTS TO THE SPECIFICATION:

Pursuant to 37 C.F.R. § 1.121, please amend the specification as follows:

Please replace the paragraph beginning at page 5, line 29 with the following amended paragraph:

In one aspect, the invention provides an isolated or recombinant polypeptide comprising an amino acid sequence of an ~~, said~~ extracellular domain (ECD) amino acid sequence having at least about 75% amino acid sequence identity to an extracellular domain amino acid sequence of, or the full-length sequence of, at least one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, and ~~is~~ not being a naturally-occurring extracellular domain amino acid sequence, and wherein said polypeptide has a CD28/CTLA-4 binding affinity ratio about equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1 and/or has an ability to induce a T-cell proliferation and/or T-cell activation response about equal to or greater than that of hB7-1. Some such polypeptides induce T-cell proliferation or T-cell activation or both T-cell proliferation and T-cell activation. In some embodiments, the T cell activation or proliferation response is at least about equal to or greater than that caused ~~cause~~ by WT hB7-1.

Please replace the paragraph beginning at page 21, line 13 with the following amended paragraph:

In one class of embodiments, any polypeptide described herein may further include a secretion signal or localization signal sequence, e.g., a signal sequence, an organelle targeting sequence, a membrane localization sequence, and the like. Any polypeptide described herein may further include a sequence that facilitates purification, e.g., an epitope tag (such as, e.g., a FLAG™ ~~FLAG~~ epitope), a polyhistidine tag, a GST fusion, and the like. The polypeptide optionally includes a methionine at the N-terminus. Any polypeptide described herein optionally includes one or more modified amino acids, such as a glycosylated amino acid, a PEG-ylated amino acid, a farnesylated amino acid, an acetylated amino acid, a biotinylated amino acid, a carboxylated amino acid, a phosphorylated amino acid, an acylated amino acid, or the like. Any polypeptide described herein further may be incorporated into a fusion protein, e.g., a fusion with an immunoglobulin (Ig) sequence.

Please replace the paragraph beginning at page 27, line 7 with the following amended paragraph:

Figures 8A-8B present schematic representations of the amino acid sequences of CD28BP-15 ~~CD28BP-13~~ and CTLA-4BP 5x4-12c and the genealogy of these sequences.

Please replace the paragraph beginning at page 27, line 9 with the following amended paragraph:

Figures 9A-9F are graphs depicting the mean fluorescence intensities generated by the binding of labeled soluble ligand sCD28-Ig and labeled soluble ligand sCTLA-4-Ig ~~sCTLA4-Ig~~ to clones CD28BP-15 and CTLA-4BP 5x4-12c. Figures 9G-9H provide graphs illustrating histograms from the staining of stable 293 transfectants expressing CTLA-4BP 5x4-12c (gray histograms), hB7-1 (gray histograms) and negative control transfectants (open histograms) with anti-hB7-1 monoclonal antibodies (mAbs) with expression levels analyzed by flow cytometry.

Please replace the paragraph beginning at page 29, line 3 with the following amended paragraph:

Figure 17 illustrates an example of a phB7-1ECD-Ig plasmid expression vector comprising a nucleotide sequence encoding a soluble extracellular domain of a human B7-1/IgG1 ~~B&-1/IgG1~~ Fc domain fusion protein. A nucleotide sequence encoding the extracellular domain of a NCSM polypeptide (or fragment thereof) can be substituted for the human B7-1-ECD sequence.

Please replace the paragraph beginning at page 43, line 14 with the following amended paragraph:

A ~~An~~ "binding affinity ratio" refers to a relative ratio of the binding affinity of a molecule of interest (e.g., a recombinant ligand, such as a NSCM polypeptide) for a first molecule (e.g., a first receptor, such as CD28 receptor) to the binding affinity of the same molecule of interest to a second molecule (e.g., a second receptor, such as CTLA-4 receptor). In one aspect, the relative binding affinity ratio may be determined by visual inspection, such as by, e.g., examining a FACS binding profile that displays the binding affinity profile of the molecule of interest to both receptors, and

evaluating the degree of relative binding of the molecule of interest to each of the first and second receptors. The results of this determination can be compared with a similar examination and evaluation of a FACS binding affinity profile displaying the binding affinity of a control molecule (e.g., wild-type ligand, such as a WT human, primate, or mammalian B7-1) to both receptors, wherein the degree of relative binding of the control molecule to each of the receptors is evaluated. These and other procedures described below can be used to determine a CD28/CTLA-4 binding affinity ratio for a CD28BP polypeptide of the present invention and a CTLA-4/CD28 binding affinity ratio for a CTLA-4BP polypeptide of the present invention. Alternatively, a binding affinity ratio can be determined by making a ratio between a quantitative measurement of the binding affinity of the molecule of interest (e.g., ligand) for the first receptor and a quantitative measurement of the binding affinity of the molecule of interest for the second receptor using known procedures for measuring binding affinities. For example, known methods for measuring the binding affinity of human (or other mammalian) B7-1 for each of CD28 and CTLA-4 receptors can be used.

Please replace the paragraph beginning at page 78, line 10 with the following amended paragraph:

It will thus be appreciated by those skilled in the art that due to the degeneracy of the genetic code, a multitude of nucleic acid ~~acids~~ sequences encoding NCSM polypeptides of the invention may be produced, some of which may bear minimal sequence homology to the nucleic acid sequences explicitly disclosed herein. Using, as an example, the nucleic acid sequence corresponding to nucleotides 1-15 of SEQ ID NO:1, ATG GGT CAC ACA ATG, a silent variation of this sequence includes ATG GGA CAT ACG ATG, both of which sequences encode the amino acid sequence MGHTM, which corresponds to amino acids 1-5 of SEQ ID NO:48.

Please replace the paragraph beginning at page 94, line 27 with the following amended paragraph:

In another aspect, the present invention provides NCSM polypeptides (e.g., full-length NCSM polypeptide, signal peptide, ECD, cytoplasmic domain, transmembrane domain, mature region, or other fragment), and fusion proteins comprising said polypeptides, having at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%

or more percent sequence identity or sequence similarity with the polypeptide of any of SEQ ID NOS:48-94, 174-252, 263-272, and 283-293 or a fragment thereof , including, e.g., one or more of a signal peptide, ECD, cytoplasmic domain, transmembrane domain, or mature region or any combination thereof. Such fragments of SEQ ID NOS:69-92, 222-272, and 286-288 may have at least one CTLA-4BP ~~CTLA4BP~~ property described herein, such as, e.g., an ability to inhibit T cell proliferation or activation in conjunction with stimulation of T cell receptor (e.g., by antigen or anti-CD3 Ab) and/or a CTLA-4/CD28 binding affinity ratio about equal to or greater than that of hB7-1. Such fragments of SEQ ID NOS:48-68, 174-221, 283-285, and 289-293 may have at least one CD28BP property described herein, such as, e.g., an ability to induce T cell proliferation or activation in conjunction with stimulation of T cell receptor (e.g., by antigen or anti-CD3 Ab) and/or a CD28/CTLA-4 binding affinity ratio about equal to or greater than that of hB7-1. Such fragments of SEQ ID NOS:93-94 may have an ability to induce T cell proliferation or activation in conjunction with stimulation of T cell receptor (by, e.g., an antigen) and/or a CD28/CTLA-4 binding affinity ratio approximately equal to that of a primate, such as hB7-1.

Please replace the paragraph beginning at page 131, line 12 with the following amended paragraph:

The invention includes a polypeptide variant of a WT or mutant B7-1 having an altered binding activity or altered binding affinity ratio compared with the binding activity or binding affinity ratio of a first B7-1 polypeptide or polypeptide fragment thereof (e.g., a polypeptide fragment corresponding to a signal peptide and/or ECD or mature domain of the first B7-1 polypeptide as described above), wherein the polypeptide variant has an amino acid sequence that differs from the amino acid sequence of the first B7-1 polypeptide (or polypeptide fragment thereof) and is ~~by~~ at least about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% homologous or identical with the amino acid sequence of the full-length hB7-1 polypeptide sequence (i.e., the second polypeptide) shown in SEQ ID NO:278 or with the amino acid sequence of a polypeptide fragment of SEQ ID NO:278, such as, e.g., a fragment corresponding to a signal peptide and/or ECD or mature domain (e.g., a fragment comprising amino acid residues 1-243, 35-243, or 35-288 of SEQ ID NO:278, respectively). The difference between the amino acid sequence of the variant and the amino acid sequence of the first B7-1 polypeptide (or fragment thereof) comprises a

different amino acid at a position corresponding to position 65 of the amino acid sequence of SEQ ID NO:278. In one aspect, the different amino acid is selected from the group of His, Arg, Lys, Pro, Phe, and/or Trp, and, preferably, comprises His. The first B7-1 polypeptide may comprise a WT B7-1 or a mutant, derivative, or conservatively substituted variant of the WT B7-1, and some such variants induce a decreased level of T cell proliferation or lack T cell proliferation compared to the level of T cell proliferation induced by hB7-1.

Please replace the paragraph beginning at page 140, line 28 with the following amended paragraph:

A CTLA-4BP polypeptide consensus sequence refers to a nonnaturally-occurring or recombinant polypeptide that predominantly includes those amino acid residues which are common to all CTLA-4BP polypeptides of the present invention (e.g., full-length and ECD polypeptides) and that includes, at one or more of those positions wherein there is no amino acid common to all subtypes, an amino acid that predominantly occurs at that position and in no event includes any amino acid residue that is not extant in that position in at least one CTLA-4BP of the invention. A CTLA-4BP consensus polypeptide may have at least one property of a CTLA-4BP polypeptide as described herein (e.g., CTLA-4/CD28 ~~CTLA-4BP/CD28~~ binding affinity ratio at least about equal to greater than that of hB7-1; suppress an immune response, or inhibit T cell proliferation or activation).

Please replace the paragraph beginning at page 142, line 19 with the following amended paragraph:

The invention also provides at least one fragment of an isolated or recombinant CD28BP polypeptide sequence selected from at least one of SEQ ID NOS:48-68, 174-221, 283-285, and 289-293, wherein the fragment binds or specifically binds with a CD28 and/or CTLA-4 ~~CTLA4~~ receptor and/or induces T cell proliferation or activation in conjunction with stimulation of a T cell receptor (e.g., by antigen) as described herein for CD28BP polypeptides, and provided the fragment itself is not an amino acid fragment known in the art to have such properties.

Please replace the paragraph beginning at page 142, line 26 with the following amended paragraph:

In addition, the invention provides at least one fragment of an isolated or recombinant CTLA-4BP polypeptide sequence selected from at least one of SEQ ID NOS:69-92, 222-272, and 286-288, wherein the fragment binds or specifically binds with a CD28 and/or CTLA-4 ~~CTLA4~~ receptor and/or inhibits T cell activation or proliferation as described herein for CTLA-4BP polypeptides, and further provided the fragment itself is not an amino acid fragment known in the art to have such properties. Fragments of SEQ ID NOS:93-94 having such properties as described for either of CTLA-4BP or CD28 polypeptides are also included.

Please replace the paragraph beginning at page 148, line 24 with the following amended paragraph:

In one typical format, the immunoassay uses a polyclonal antiserum which was raised against one or more NCSM polypeptides comprising one or more of the sequences corresponding to one or more of SEQ ID NOS:48-94, 174-252, 263-272, and 283-293, or a substantial subsequence or fragment thereof (i.e., comprising at least about 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the amino acids of the full length sequence provided). The full set of potential polypeptide immunogens derived from SEQ ID NOS:48-94, 174-252, 263-272, and 283-293 are collectively referred to herein as "the immunogenic polypeptides." The resulting antisera is optionally selected to have low cross-reactivity against the control, e.g., co-stimulatory homologues and any such cross-reactivity is removed by immunoabsorption ~~immunoabsorbtion~~ with one or more of the control polypeptides, prior to use of the polyclonal antiserum in the immunoassay. Sequences which are substantially identical to such sequences can also be used, e.g., which are at least about 60%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identical, e.g., as determined using BLAST or the other algorithms described herein and above, e.g., using default parameters.

Please replace the paragraph beginning at page 186, line 28 with the following amended paragraph:

The CTLA-4BPs ~~CTLA4BPs~~, or fragments thereof or soluble and/or fusion proteins thereof, of the invention can modulate T cell proliferation and/or activation and inhibit the immune response in autoimmune diseases or, as soluble molecules, act as antagonists. Such a CTLA-4BP polypeptide can be delivered in a treatment protocol as a component of a DNA vaccine vector, as a full-length

polypeptide, as a soluble polypeptide subsequence of the full-length CTLA-4BP polypeptide (e.g., ECD) used, if desired, as a polypeptide or protein vaccine or "boosting" polypeptide, or as a soluble fusion protein comprising a full-length CTLA-4BP polypeptide or subsequence thereof, such as a soluble polypeptide subsequence (e.g., ECD); in such formats, the CTLA-4BP polypeptide may serve as an agonist.

Please replace the paragraph beginning at page 187, line 5 with the following amended paragraph:

As discussed above, genetic vaccine comprising a vector comprising a nucleic acid sequence encoding a CTLA4-BP polypeptide and at least one nucleic acid sequence encoding at least one additional polypeptide of interest is also a feature of the invention. For example, in a DNA vaccine, in combination with a specific allergen, the CTLA-4BPs ~~CTLA4BPs~~ (or fragments thereof, or soluble and/or fusion proteins thereof) may inhibit the allergen specific T cell response in allergy. Similarly, in combination with a specific auto-antigen, such as myelin basic protein, the CTLA-4BPs (or fragments thereof, or soluble and/or fusion proteins thereof) may inhibit the auto-antigen-specific T cell response in autoimmunity, such as in multiple sclerosis.

Please replace the paragraph beginning at page 212, line 17 with the following amended paragraph:

Fifty R2 CTLA-4BP clones were found to have preferential binding to CD28 over CTLA-4 as shown in both individual and competitive binding assays between cells transfected with these clones and fluorescently labeled soluble CD28-Ig fusions and/or CTLA-4-Ig ~~CTLA4-Ig~~ fusions. Exemplary binding profiles for selected clones are shown in Figures 7A-7H. The respective amino acid and nucleic acid sequences of the clones were determined (Table 4). Table 4 presents a summary of the relative binding activities of these selected 50 R2 CTLA-4BP clones based on the three exemplary binding profiles shown in Figs. 6A(1)-6A(3). In the three exemplary competitive binding profiles, the Y-axis represents binding to CD28, and the X axis represents binding to CTLA-4 (see binding assays described in "Materials and Methods"). An exemplary binding profile for the binding of WT B7-1 to CD28 and CTLA-4 is shown in Fig. 6A(1), indicating approximately equal binding affinity of WT B7-1 to CD28 and CTLA-4. An exemplary binding profile indicating for a particular clone a preferential binding to CTLA-4 over CD28 relative to that of WT B7-1 is shown in

Fig. 6A(3); the clone has a CTLA-4/CD28 ~~CTLA4/CD28~~ binding affinity ratio significantly greater than the CTLA-4/CD28 binding affinity ratio of WT hB7-1. An exemplary binding profile indicating intermediate preferential binding to CD28 over CTLA-4 relative to that of WT B7-1 is shown in Fig. 6A(2); the clone has a CTLA-4/CD28 ~~CTLA4/CD28~~ binding affinity ratio greater than that of WT hB7-1.

Please replace the paragraph beginning at page 216, line 10 with the following amended paragraph:

Figures 8A-8B show the respective amino acid sequences for CD28BP-15 ~~CD28BP-12~~ and CTLA-4BP 5x4-12c and the genealogy of these sequences. The nucleotide and amino acid sequences for each of CD28BP-15 ~~CD28BP-12~~ and CTLA-4BP 5x4-12c were aligned with the starting genes to identify the parental origins of the recombinant sequences. The chimeric nature of each recombinant amino acid sequence is indicated by a solid labeled line designating each amino acid subsequence derived from a particular parental species sequence. Any amino acid residue that differs from a residue in the WT human B7-1 sequence in the corresponding (equivalent) amino acid residue position is indicated with a star (*). Three point mutations in CTLA-4BP 5x4-12c that were not derived from any of the starting parental genes are indicated with a solid triangle. The predicted transmembrane domain is illustrated with a dashed line (prediction based on equivalent analysis for mammalian B7-1 molecules in Parsons, K.R. & Howard, C.J. (1999) Immunogenetics 49:231-4).

Please replace the paragraph beginning at page 219, line 1 with the following amended paragraph:

The binding of labeled soluble ligand sCD28-Ig and sCTLA-4-Ig ~~sCTLA4-Ig~~ to clones CD28BP-15 and CTLA-4BP 5x4-12c was further studied, as shown in Figures 9A-9H. Specifically, 293 cells were transiently (Figs. 9A-9B) or stably (Figs. 9C-9D) transfected with CD28BP-15 (solid circles) or hB7-1 (open squares), and with (dashed lines) and without (solid lines) a FLAG™ tag ~~FLAG-tag~~. 293 cells were stably transfected with CTLA-4BP 5x4-12c (solid triangles) or WT hB7-1 (open squares) (Figs. 9D-9E). Cells transiently (Figs. 9A-9B) or stably (Figs. 9C, 9D, 9E, 9F) transfected with a vector lacking a WT hB7-1, CD28BP or CTLA-4BP nucleic acid insert were used as negative controls (open diamonds). The transfectants were stained with increasing concentrations of labeled soluble CD28-Ig (Figs. 9A, 9C, 9E) or soluble CTLA-4-Ig (Figs. 9B, 9D, 9F), prepared as

described above, and the cells were analyzed by flow cytometry. Stable 293 transfectants expressing CTLA-4BP 5x4-12c (gray histograms), hB7-1 (gray histograms) and negative control transfectants (open histograms) were stained with anti-hB7-1 mAbs (Figs. 9G-9H), and the expression levels were analyzed by flow cytometry.

Please replace the top header of Table 6 beginning on page 227, line 27 (header of Table 6) with the following:

Table 6

Clone ID	Nucleotide Position	Amino Acid Position ~~Postion~~	3' end ECD